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Art Unit: 1624 )  
 )  
Examiner: Balasubramanian, ) October 30, 2002 *Patricia Muñoz*  
 ) Venkataraman ) Patricia Muñoz

AMENDMENT UNDER 37 C.F.R. § 1.111

Commissioner for Patents  
Washington, D.C. 20231

Sir:

In response to the Office Action mailed May 30, 2002 which rejected claims 1 to 10, 13 to 15, 17 to 29, 33 to 38, 41 to 46 and 49, and indicated that claims 11, 12, 16, 30 to 32, 39, 40, 47 and 48 were withdrawn from consideration, Applicants make the following amendments and remarks.

In the Claims

Please amend claims 1, 10, 11, 14, 18, 33, 39, 40, 47 and 48 as shown in the attached "Claims Marked Up to Show Changes."

Please cancel claims 9, 13, 16, 17, 30, 31 and 32.

Please add new claims 50 to 56.

Also submitted herewith are "Clean Claim Sheets" with the claims as pending after entry of the present amendments.

REMARKS

The Office Action mailed May 30, 2002 set an initial three (3) month period for response. Applicants note that submitted

herewith is a Petition under 37 C.F.R. § 1.136(a) for a two-month extension of time and a check which includes the required fee. With the granting of this Petition, the time period in which to submit a timely response to the Office Action mailed May 30, 2002 will be extended to October 30, 2002.

Applicants note that also submitted herewith are Formal Drawings as required by the Notice of Draftperson's Patent Drawing Review (PTO-948) which was an attachment to the Office Action mailed May 30, 2002.

#### The Pending Claims

Claims 1, 10, 11, 14, 18, 33, 39, 40, 47 and 48 have been amended to more particularly point out and distinctly claim aspects of Applicants' invention. Claims 9, 13, 16, 17, 30, 31 and 32 have been cancelled without prejudice to expedite prosecution. Applicants reserve their rights to pursue subject matter deleted from the cancelled claims and the subject matter of the cancelled claims in continuing and/or divisional applications as appropriate. New claims 50 to 56 have been added.

Applicants note that the Examiner had indicated that claims 1 to 49 were pending, but that claims 11, 12, 16, 30 to 32, 39, 40, 47 and 48 were drawn to a non-elected invention. Applicants note that claims 11, 12, 39, 40, 47 and 48, as amended are now drawn to the elected invention of Group II and claims 16 and 30 to 32 have been cancelled.

Claims 1, 10, 11, 14, 18, and 33 have been amended and new claims 50 to 56 have been added to more particularly point out and distinctly claim the compounds of provisionally elected Group II and to delete subject matter of the non-elected invention of Group I. Claims 39, 40, 47 and 48, previously

dependent on cancelled claims 31 or 32, have been amended to be dependent on new claims 53 or 55. Applicants submit that these amendments are clearly supported by the specification and claims as originally filed and give rise to new issue of new matter.

The Examiner's Revised Restriction Requirement

Applicants note the Examiner's revision of the Restriction Requirement which was originally made in the Office Action mailed January 9, 2002, with respect to which claims were included in Group I and which claims were included in Group II.

As revised by the Examiner and as set forth in the Office Action mailed May 30, 2002, the Examiner required restriction to one of the following inventions:

Group I: Claims 1 to 8, 11 to 12, 16, 30 to 36, 39 to 44 and 47 to 48, drawn to compounds of Formula I where  $Q=N$ , and

Group II: Claims 1 to 10, 13 to 15, 17 to 29, 33 to 38, 41 to 46 and 49, drawn to compounds of Formula I where  $Q=C(R_4)$ .

Applicants confirm that, in response to the Examiner's revised restriction requirement, they have provisionally elected to prosecute the invention of Group II, with traverse.

Applicants submit that the genus as set forth in the claims as originally filed was properly examinable as a whole without undue burden on the Examiner. Applicants note that in order to expedite prosecution and allowance of claims directed to the invention of provisionally elected Group II, they may have amended the claims to focus on the compounds of elected Group II.

The Section 112, Second Paragraph Rejection of Pages 4 to 5

Claims 1 to 10, 13 to 15, 17 to 29, 33 to 38, 41 to 46 and 49 stand rejected under 35 U.S.C. §112, second paragraph, as assertedly indefinite.

This rejection is respectfully traversed. Although Applicants submit that the claims as pending prior to the present amendments were in compliance with the requirements of the second paragraph of Section 112, Applicants note that claims 1, 10, 11, 14, 18, and 33 have been amended to more particularly point out and distinctly claim aspects of Applicants' invention and also to deal with certain comments regarding terminology made by the Examiner.

Applicants request that the Examiner reconsider the present rejection and withdraw it.

The Section 112, First Paragraph, Rejection of Pages 5 to 9

Claims 34 to 49 stand rejected under 35 U.S.C. §112, first paragraph, as assertedly nonenabled.

This rejection is respectfully traversed. Applicants submit that the Examiner's position is not well taken and that claims 34 to 49 as presently pending, clearly comply with the first paragraph of Section 112.

Applicants do not fully understand certain portions of the Examiner's rationale for this rejection and requests appropriate clarification should this rejection be maintained.

Applicants note that the Examiner appears to assert that Applicants do not reasonably provide enablement for prevention and makes the following assertions in support of his position:

The instant claims are drawn to 'a preventive and/or remedy for thrombosis or embolism' and various diseases related to

thrombosis including cerebral infraction, cerebral embolism, myocardial infraction, deep vein thrombosis etc. The scope of the claims includes not only treatment (note remedy is synonymous with treatment) but also "prevention" of diseases which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 354-365. The instant compounds are disclosed have FXa inhibitory activity which relates to inhibition of thrombin and it is recited that the instant compounds are useful in 'treating or preventing' several diseases, for which applicants provide no competent evidence. "To prevent" actually means *to anticipate or counter in advance, to keep from happening* etc. (as per Websters II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

Office Action mailed May 30, 2002 at page 6.

Applicants note that a number of the assertions made by the Examiner in the portion of the Office Action quoted above do not appear to be well taken.

In stating his position regarding alleged lack of enablement of claims drawn to "prevention", Applicants note that the Examiner puts the following phrase in quotation marks:

a preventative and/or remedy for thrombosis  
or embolism

Id. Applicants request that the Examiner identify the source for the above-noted phrase and provide clarification regarding his concern.

Applicants also note that the Examiner refers to "compounds provided in the specification at pages 354-365." Applicants note that the application as filed included 83 pages of specification (pages 1 to 83), 11 pages of claims (pages 84 to 94), one page of abstract (page 95) and 2 sheets of drawings. Accordingly, Applicants do not understand Examiner's reference to pages not in the page range of the present application and request appropriate clarification.

Applicants also note the Examiner's apparent assertion regarding "FXa inhibitory activity." Applicants note that Applicant's compounds are described as selective inhibitors of thrombin and that they provide appropriate support for their activity.

Claims 34 to 49 are directed to "pharmaceutical compositions for treating or decreasing the incidence" (claims 34 to 41) and to "methods of treating or decreasing the incidence" (claims 42 to 49) of a condition characterized by abnormal thrombosis using a compound of Applicant's invention. Applicants note that the Examiner appears to equate "decrease the incidence of" with "prevent." Applicants submit that the Examiner appears to be construing the term "decrease the incidence" quite differently from how that term would be construed or understood by one of skill in the art. One of skill in the art would not understand Applicants' use of "decrease the incidence" to require absolute "prevention" which appears to be the Examiner's interpretation of the phrase.

Applicants submit that the Examiner's position with regard to the assays described in the specification at pages 78 to 83 and their import is also not well taken. The assays described at pages 78 to 83 are *in vitro* assays which are art-recognized as reasonably predictive of *in vivo* activity. Activity

demonstrated in assays such as those described in Example A is used to select compounds for further study in animal models, and, possibly, eventual clinical trials.

Applicants note the Examiner's citation of the Revised Interim Utility and Written Description Guidelines in apparent support of the present rejection. Applicants submit that this citation is not germane to the present rejection. Moreover, from a reading of the guidelines, Applicants appear to be in compliance. Applicants note that the invention, as claimed by claims 34 to 49, has a specific and substantial utility which is credible to one of ordinary skill in the art in view of Applicants' disclosure and the knowledge and level of skill in the art.

Applicant's attorney has reviewed the references (one page abstracts of much longer articles from scientific journals) cited by the Examiner to support his position: Rauch, et al., "Thrombus formation on atherosclerotic plaques: pathogenesis and clinical consequences", *Ann. Intern. Med.* 134(3):224-38 (Feb. 6, 2001) ("Rauch, et al.") and Van Aken, et al., "Anticoagulation: the present and future", *Clin. Appl. Thromb. Hemost.* 7(3):195-204 (July 2001) ("Van Aken, et al."). Applicants submit that these references actually support enablement of claims 34 to 49.

Applicants note that both Rauch, et al. and Van Aken, et al. appear to summarize certain current antithrombotic and anticoagulation therapies and potential therapies.

Applicants note that Rauch, et al. note that thrombin inhibitors are being evaluated as possible options for the treatment of arterial thrombosis and suggest that such therapies may effectively block thrombosis without causing bleeding complications.

Applicants note that Van Aken, et al. discuss presently used and potential future anticoagulant therapies for treatment of thromboantibolic conditions. In particular, Van Aken, et al. mention that reversible noncovalent direct thrombin inhibitors have potential as safer and more specific therapies, including use in the prophylaxis and treatment of thrombosis.

In particular, Applicants note that the thrombin inhibitors within the scope of claims 34 to 49 are noncovalent direct thrombin inhibitors.

Applicants request that the Examiner reconsider this rejection in view of the above and withdraw it.

#### CONCLUSION

In view of the foregoing, Applicants submit that all the rejections of claims 1 to 10, 13 to 15, 17 to 29, 33 to 38, 41 to 46 and 49 have been overcome and that those claims are allowable. Applicants submit that claims 11, 12, 39, 30, 47 and 48, now drawn to the elected invention of Group II, are also allowable. Applicants submit that new claims 50 to 56 are allowable as well. Applicants request that the claims be allowed and passed to issue.

If the Examiner believes that a telephonic interview would expedite allowance of this application, he is encouraged to telephone Applicants attorney of record, Suzanne L. Biggs at the below-noted telephone number.

The Commissioner is hereby authorized to charge any fee, including any fee due with this submission, if the attached check(s) is in the wrong amount or otherwise improper or missing, that may be due in connection with this and the attached papers, or with this application during its entire



pendency to or to credit any overpayment to Deposit Account 03-3975, Order No. 018813-0272492.

Respectfully submitted,  
PILLSBURY WINTHROP LLP

By 

Suzanne L. Biggs

Registration No. 30,158

Dated: October 30, 2002

Attorney Docket No. 018813-0272492

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